Topics in Primary Care Medicine

Osteoarthritis
A Continuing Challenge

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Osteoarthritis is a disorder of cartilage that affects almost 85% of the population by age 75. A lack of rigorous clinical and radiographic criteria for defining the disorder makes precise determination of its prevalence impossible. The process of wear and tear explains many manifestations of osteoarthritis, but it does not account for some of the clinical findings or the biochemical changes in osteoarthritic cartilage. Thus, other factors such as heredity, hormones, and diet may play a role. Treatment consists of teaching patients about their disease, alleviating pain, and preserving joint function. Nonsteroidal anti-inflammatory drugs may be no more effective than simple analgesics in relieving the pain of this disorder. Moreover, some nonsteroidal anti-inflammatory drugs can adversely affect cartilage metabolism, and most are possibly dangerous in elderly patients. Drugs that inhibit the production or activity of chondrolytic enzymes can slow the degeneration of cartilage in some animals, but their effects on humans with osteoarthritis are unproved. The surgical repair of severely damaged joints can have gratifying results.

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Osteoarthritis is in many ways like the weather—ubiquitous, often unnoticed, sometimes dramatic in its effects, and largely unexplained. To carry the analogy further, everyone talks about osteoarthritis, but nobody seems to be doing much about it.

The name may be a misnomer. The disorder's primary cause is not likely to reside in bone,[1,2] and inflammation is not prominent in its initial stages.[3] Nevertheless, the term osteoarthritis serves its purpose—it is short, physicians and patients know what it means, and it has a more benign connotation for patients than does "degenerative joint disease."

The prevalence of osteoarthritis in the population is hard to determine because the disorder cannot be defined precisely. Do all patients with joint pain and radiographic evidence of osteophytes have osteoarthritis?[4,5] Does a normal radiograph exclude its diagnosis in a patient with joint pain?[6] Can osteoarthritis be completely asymptomatic?[7] Are osteophytes a normal consequence of aging?[4] Will our ability to quantify cartilaginous loss with magnetic resonance imaging scans alleviate or enhance our confusion?[8]

Osteoarthritis rarely occurs before age 40, but by age 75, at least 85% of the population have either clinical or radiographic evidence of the disease.[9] Although it occurs more frequently and tends to affect more joints in women, for those younger than 45, it affects both sexes equally.[10] White populations from developed countries have similar rates of osteoarthritis in the hands and the knees.[10] By contrast, black American women have more osteoarthritis of the knees.[11] Although it is relatively uncommon (less than 5%) in the hips in Chinese[12] and in most black populations,[13] its prevalence in many European communities approaches 25%.[13]

What Causes Osteoarthritis?

For many years, investigators have embraced the concept that osteoarthritis is a disease of wear and tear. Some of its clinical manifestations do not fit this notion, however. For instance, why do women have a propensity for prominent bony enlargement of the distal interphalangeal (Heberden's nodes) and proximal interphalangeal (Bouchard's nodes) joints,[14] whereas men who do manual labor show no such predisposition for the disease in their hands?[15,16] Why does an inflammatory form of osteoarthritis tend to affect women near menopause?[17-19] And why is cartilage in patients with the disorder biochemically different from cartilage in older people without it?[20]

Understanding the structure and function of normal cartilage may provide some clues to the pathogenesis of osteoarthritis. Articular cartilage provides a low-friction bony interface greatly capable of absorbing shock. These functions are dependent on the composition of the cartilage matrix, which consists of collagen fibers (which make up 50% of the dry weight of cartilage) intermingled with proteoglycans—high-molecular-weight aggregates of glycosaminoglycans (mucopolysaccharides) bound to protein chains (Figure 1).[20-22] From a functional standpoint, collagen gives cartilage tensile strength and allows it to resist shear forces occurring during motion under

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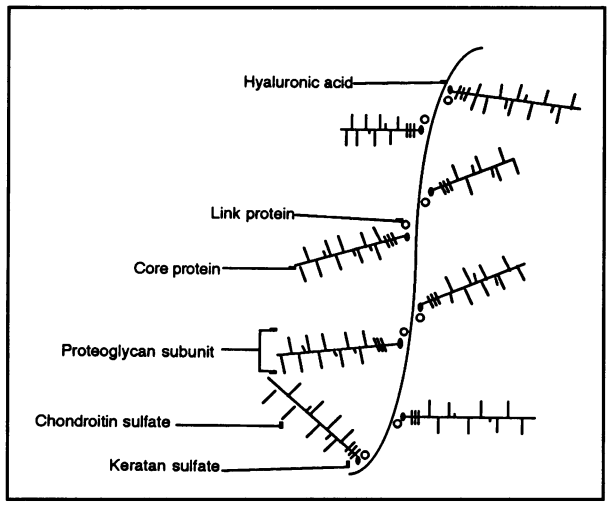

Figure 1.—A schematic representation of a proteoglycan aggregate is shown.

load. Collagen also constrains the negatively charged hydrated proteoglycans. This produces a large swelling pressure and gives cartilage its elasticity and resistance to compression.[21] Under high-load conditions, proteoglycans release water and provide lubrication at the cartilage surface (hydrostatic lubrication).[20,21] Not surprisingly, areas of cartilage that are subjected to heavy loads contain greater concentrations of proteoglycans.[23,24]

Damage to the collagen fibers or to the proteoglycan matrix of cartilage causes a loss of its normal lubricating and shock-absorbing functions. Unfortunately, cartilage responds poorly to injury because of a limited blood supply and the lack of undifferentiated mesenchymal cells capable of initiating healing. Thus, repair tends to be spotty, and instead of containing collagen found in normal articular cartilage, the newly formed cartilage contains collagen characteristic of fibrocartilage.[25]

The cartilage in patients with osteoarthritis is not simply "old and worn out" (Table 1). Compared with normal cartilage, aging cartilage contains less water, a higher ratio of keratan to chondroitin sulfate, and fragmented link protein. Yet, there is no evidence that aging cartilage is biochemically inferior to normal cartilage. Cartilage in patients with osteoarthritis, on the other hand, contains more water, less keratan sulfate than in normal cartilage, and normal link protein.[20] Structural changes in the proteoglycan macromolecules are key features of osteoarthritis and, together with ultrastructural changes in collagen fibers, cause deterioration in the function of cartilage. The chondrocyte, previously thought to be an inert cell, is likely an important participant in this process. It has anabolic or catabolic functions, depending on local events. In contrast to rheumatoid arthritis where the synovium is the primary source of proteolytic enzymes, in osteoarthritis the chondrocyte seems to be the principal producer of these substances.[26,27] Table 2 contains a partial list of cytokines likely to be important in the pathogenesis of osteoarthritis.[27,28]

TABLE 1.—*Composition of Aging Cartilage Versus That Affected by Osteoarthritis**

Chemical Composition	*Aging Cartilage*	*Osteoarthritic Cartilage*
H_2O	↓	↑
Glycosaminoglycans	Normal or slightly ↓	↓
Keratan sulfate	↑	↓
Chondroitin sulfate	↓	Early ↑, then ↓
Hyaluronic acid	↑	↓
Proteoglycans	†	‡
Link protein	Fragmented	Normal

↓ = amount decreased, ↑ = amount increased

*Modified from Brandt and Fife.[20]
†Decreased extractability and normal aggregation.
‡Increased extractability and decreased aggregation.

TABLE 2.—*Cytokines in Osteoarthritis*

Cytokine	*Effect*
Interleukin (IL) 1	Stimulates loss of proteoglycan (PG) from cartilage, release of proteases, synthesis of IL-6 and type I collagen Inhibits cell division in chondrocytes, synthesis of type II collagen
Interferon gamma	Suppresses synthesis of type II collagen
Tumor necrosis factor alpha	Stimulates synthesis of proteases
IL-6	Inhibits IL-1–induced breakdown of cartilage and synthesis of cartilage PG Stimulates production of tissue inhibitor of metalloproteases (TIMP)
Transforming growth factor beta	Stimulates synthesis of collagen and TIMP Inhibits synthesis of collagenase
Insulin-like growth factor I	A potent anabolic factor of cartilage

Role of Trauma

Could trauma initiate these biochemical events? Although loading and motion are important in preserving normal cartilage metabolism and function,[29-33] exerting excessive force on cartilage can have the opposite effect.[34-36] Thus, activities such as jumping or twisting can damage articular cartilage, and an injury that results in an unstable joint or that damages the normal cushioning structures, such as a meniscus in the knee, can render cartilage vulnerable to stress. It has been suggested that trauma to cartilage can be more subtle. Indeed, a subset of the normal population habitually loads their legs at heel strike and thus may be predisposing themselves to joint damage.[35] Having abnormally dense bone could also predispose cartilage to injury,[37-41] but this idea has been disputed.[42-44] Finally, an intact neuromuscular system is important in maintaining normal joint function. Although deficits in sensory nerves are not an important cause of osteoarthritis, abnormalities in the muscular reflex that

normally protects the joints could increase its severity.[45]

In 1971 a mechanism was proposed for the occurrence of "nodal" osteoarthritis in women.[15] It was postulated that the smaller surface area of the distal joints of the fingers subjects these joints to greater pressures per square inch than the more proximal joints. Furthermore, fine motor activity uses the deep flexor tendons that insert into the distal phalanges, but these tendons are "splinted" by the superficial tendons during power-grip activities. Thus, knitting and sewing would likely produce more node formation than hammering and sawing. It was subsequently shown that in an industrial setting, node formation in the fingers correlated more with repetitive, fine motor activity than with gender.[16]

Role of Heredity

Early studies suggested that generalized osteoarthritis, which typically affects the hands, knees, and spine, occurs in two forms—one in association with Heberden's nodes, the other without such nodes.[46-48] Nodal osteoarthritis showed an inheritance pattern consistent with an autosomal gene, dominant in females and recessive in males.[49,50] Non-nodal osteoarthritis showed a polygenic inheritance.[51] Lacking in these studies, however, is information regarding occupation and other physical activities involving the hands. Current research has linked abnormalities in the type II procollagen gene *COL2A1* on chromosome 12 with some familial forms of generalized erosive osteoarthritis.[52,53] Patients with these abnormalities typically have an associated chondrodystrophy, however. Such genetic defects do not account for most cases of osteoarthritis.[54]

Role of Estrogen

The predisposition of women to severe osteoarthritis and the tendency for the inflammatory form to occur near menopause suggest that estrogens play a role in this disorder.[55] Indeed, the articular cartilage of some animals contains estrogen receptors.[56-58] Whether estrogens alleviate or worsen the disease in animals seems to depend on the model being studied.[59,60] Possibly detrimental effects of estrogens on cartilage include suppressing chondrocyte proliferation, suppressing proteoglycan synthesis, and stimulating cytokine release from macrophages and chondrocytes.[61]

Role of Diet

How might diet affect the development or severity of osteoarthritis? Certainly obesity plays a role in the occurrence and progression of the disease in the knees.[62-66] This could be ascribed to the mechanical effect of increased weight, but it is hard to understand why obesity is a modest predictor of osteoarthritis in the distal interphalangeal and first carpometacarpal joints.[67] In some animal models, a diet high in saturated fat increases the severity of the disease,[68-70] but in other studies this effect has been hard to reproduce.[71] Some secondary forms of osteoarthritis have a presumed dietary association.[72] Kashin-Beck disease, for example, is a noninflammatory disorder of enchondral bone growth endemic to eastern Siberia, northern China, and northern Korea. Dystrophic changes in the epiphyseal and metaphyseal areas lead to secondary degenerative changes in peripheral joints and the spine. Proposed causes have included infectious agents and excesses or deficiencies of trace elements.[72-74]

Clinical Aspects of Osteoarthritis

Osteoarthritis affects most movable joints. Pain in a joint with movement along with articular bony enlargement are typical manifestations of, but are not specific for, the disease. Nevertheless, certain aspects of joint involvement are fairly consistent and deserve mention.

In the hands, osteoarthritis affects primarily the distal interphalangeal, proximal interphalangeal, and first carpometacarpal joints (Figure 2). Deformity or a decrease in motion of the joint occurs gradually, and deviation tends to be in a lateral direction, unlike the vertical deformity of rheumatoid arthritis. Metacarpophalangeal involvement is distinctly unusual, but elderly patients with extensive osteoarthritis of the hands occasionally have mild swelling or subluxation of the metacarpophalangeal joints. Heavy manual labor also may cause degenerative changes in these joints.[75]

The wrists are virtually never involved, and if they are, this should suggest another diagnosis such as rheumatoid arthritis or pseudogout. Involvement of the first carpometacarpal joint, however, may give the wrist a "squared-off" appearance (see Figure 2).

Although osteoarthritis rarely affects the elbows in the absence of a metabolic disease or previous trauma, a subset of patients may have involvement of the elbows. These patients typically are men who have osteoarthritis in other joints, particularly the metacarpophalangeal joints.[76]

Osteoarthritis frequently affects the acromioclavicular joint. By contrast, the glenohumeral joint is not a common target. When degenerative changes occur in this joint, patients are likely to have a severe tear in the rotator cuff, allowing superior migration of the humeral

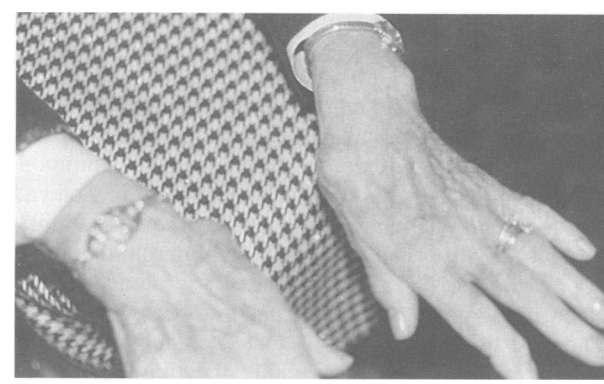

Figure 2.—Bony enlargement is seen of the distal interphalangeal joint of the index finger (Heberden's node) of a patient with osteoarthritis of the hand. The prominent first carpometacarpal joint gives the hand a squared-off appearance.

head.[77] Elderly women are susceptible to a destructive arthropathy of the shoulder ("Milwaukee shoulder"), presumably mediated by apatite crystals.[78]

Movable portions of the spine are susceptible to degenerative changes. The central gelatinous portion of the intervertebral disc (nucleus pulposus) gradually disappears with aging and is essentially nonexistent after age 45.[79] Thus, "degeneration" of discs is a normal phenomenon of aging. In the lower five cervical vertebrae, such changes could place abnormal stress on the posterior (zygoapophyseal) vertebral articulations, resulting in joint-space narrowing, subarticular sclerosis, and osteophyte formation—the hallmarks of osteoarthritis. Because the cervical spine is reputed to move about 600 times in an hour (whether awake or asleep), it is no wonder that at any given time about 10% of the population has a pain in the neck.[80] Although radiographs of the cervical spine typically show bony abnormalities of the facet joints and the posterolateral uncinate processes, caution must be used in ascribing pain in the neck or radicular symptoms to such changes.[81]

Osteoarthritis affects the hips (often both) more commonly in men than in women.[82] Heavy lifting might increase the risk of disease in this joint.[83] Other possible risk factors include leg-length discrepancy (the long leg will be affected), acetabular dysplasia, a slipped femoral epiphysis, and Legg-Calvé-Perthes disease. Most of the time, however, the cause is not apparent.[84] Pain from osteoarthritis in the hips typically occurs in the groin or anterior thigh, but occasionally in the buttock or even in the knees. Range of motion in the hip, particularly internal rotation, becomes limited. Weakness in the hip abductor muscles makes it difficult to keep the pelvis level during walking and causes a patient to tilt toward the affected side to swing the opposite leg forward (Trendelenburg gait).

The prevalence of osteoarthritis in the knees rises with age.[65,82,85] Although a third of people older than 65 have radiographic findings in the knee consistent with the disease, only 10% of this age group has pain in the knees and an abnormality of cartilage by visual or radiographic examination.[65,85] Obesity correlates strongly with osteoarthritis of the knees, particularly in women and in patients with disease of both knees.[64] Obese patients and those with a previous meniscectomy have more involvement of the tibiofemoral than the patellofemoral compartment.[66] Isolated patellofemoral disease is more common in young adults, either as a result of trauma or, in women, from recurrent patellar subluxation.[86] Although habitual physical activity of many types, including running, does not predispose to disease in the knees,[87,88] prolonged or repeated kneeling and squatting appear to be risk factors.[36] Characteristic physical findings include pain or crepitance on joint motion, tenderness along the tibiofemoral or patellofemoral articulations, and genu valgum (knock-knee) or genu varum (bowleg) deformity.

In the absence of repetitive trauma or chronic ligamentous injury, osteoarthritis seldom affects the ankles.[82,87,89] The first metatarsophalangeal joint, however, is a common target. Inflammation of the bursa overlying the medial aspect of this joint may produce a characteristic swelling (bunion).

TABLE 3.—*Other Conditions Causing Degeneration of Cartilage**

Cause	*Condition*
Inflammatory diseases	Rheumatoid arthritis Infection
Physical factors	Trauma—physical injury, obesity, mechanical derangement, neuropathic joint Ischemic necrosis of bone
Endocrine diseases	Diabetes mellitus Acromegaly
Metabolic diseases	Hemochromatosis Wilson's disease Ochronosis Crystalline—urate, calcium pyrophosphate, hydroxyapatite arthropathy
Nutritional (?)	Kashin-Beck disease Steroid injections (?)

*Modified from Sack.[97]

Looking at the pattern of osteoarthritis, the impression is that humans may have evolved faster than their joints could adapt.[90,91] After all, we developed an opposable thumb, assumed an upright posture, and learned to live well beyond our reproductive years. And we cannot regenerate new limbs.

Variations of Osteoarthritis

A "nodal generalized" form of osteoarthritis affects principally the distal and proximal interphalangeal and first carpometacarpal joints of the hands, but it also involves the hips, knees, metatarsophalangeal joints, and the spinal articulations.[46,48] Joint inflammation and exaggerated osteophyte formation can occur. An "erosive" type of osteoarthritis shows many features of generalized disease, but joint inflammation and subchondral erosive changes are more pronounced.[92-94] Patients with this form of the disease are typically women who have recently entered menopause.[55,95] The female predilection for nodal generalized osteoarthritis and the reported association of this disorder with the HLA-A1, B8 tissue type, Sjögren's syndrome, and thyroid disease suggest that this is an autoimmune disorder.[96]

When osteoarthritis occurs at atypical sites or is unusually severe, other factors may be operative (Table 3).[97] As a rule, any physical, inflammatory, or metabolic insult can predispose cartilage to further degenerative change. Particularly noteworthy is the occurrence of severe osteoarthritis in association with the deposition of calcium pyrophosphate dihydrate or apatite crystals.[98,99]

Laboratory Evaluation

Osteoarthritis causes few, if any, abnormal laboratory values. The erythrocyte sedimentation rate is typically normal but may show a modest increase in patients with

inflammatory osteoarthritis. Tests for rheumatoid factor or antinuclear antibodies are often positive in normal aging persons and therefore have little meaning when the clinical findings suggest only osteoarthritis. Synovial fluid obtained from joints affected by the disease typically shows normal viscosity and few leukocytes ($<2 \times 10^9$ per liter [2,000 per mm^3]) with a normal differential count (<0.3 [30%] polymorphonuclear cells). In rare cases, fluid from joints that have severe degeneration of cartilage or an associated deposition of crystals (such as calcium pyrophosphate dihydrate or apatite) will show a higher leukocyte count.

Radiographs in patients with osteoarthritis may show narrowing of the joint space, a marginal overgrowth of bone (osteophytes), subchondral bony sclerosis or cyst formation, or malalignment of the joint. Although these findings frequently constitute criteria for the diagnosis, they do not always correlate with clinical symptoms or with the condition of articular cartilage on arthroscopy.[100,101] Some radiographic changes, however, have prognostic importance. Thus, in hips, supralateral migration of the femoral head may carry a worse prognosis than medial migration.[102] Magnetic resonance imaging may show degenerative changes in cartilage when the plain radiograph does not.[103] Such studies are costly, however, and are useful only when planning surgical intervention.

Treatment

Grandma Moses treated her arthritis with sweet milk and turpentine.[104] The question is, can we do any better now? If the goal is to repair damaged cartilage, the answer is clearly no. If, however, the goal is to teach patients about their disease, alleviate pain, preserve joint function, or ultimately repair a severely damaged joint, then the answer is yes.

We can now provide patients a clearer picture of their long-term prognosis. For instance, studies show that osteoarthritis seldom impairs function of the hand, even if some pain and stiffness persist.[105,106] Furthermore, pain in the knees or hips may diminish as patients reach their mid-60s, even if damage to these joints is substantial.[107,108] And never underestimate the power of reassurance. In one study, patients who had monthly phone calls from lay personnel to discuss self-care issues had a substantial reduction of joint pain.[109]

Physical modalities provide the cornerstone for managing osteoarthritis. Activities that involve normal loading of joints are important in maintaining healthy cartilage.[29-33] A knowledgeable physical or occupational therapist can teach patients how to exercise safely and how to protect their joints while doing routine activities of daily living. For patients with disease of the hips, the simple measure of splitting heavy loads and carrying them in each hand, or carrying the load ipsilateral to the affected hip, will minimize the force exerted on that joint.[110] In osteoarthritis of the knees, weakness of the quadriceps muscle[111] and obesity correlate with symptoms.[62-67] Thus, sensible treatment would include muscle strengthening[112] and weight reduction.[113] Modifying shoes will occasionally improve the mechanics in knees[114] and relieve pain. Although it is hard to prove that physical modalities alter the course of osteoarthritis, such intervention may at least lessen symptoms. Two recent articles review the principles of exercise for patients with osteoarthritis.[30,115]

The cause of pain in this disease is conjectural.[116,117] Cartilage contains no nerve fibers, and synovitis does not always correlate with symptoms. Thus, it is no surprise that NSAIDs may be no better than simple analgesics like acetaminophen at relieving the pain of osteoarthritis.[118-121] Some NSAIDs adversely affect proteoglycan metabolism and could theoretically inhibit repair mechanisms in cartilage, but the effect of any particular NSAID on the eventual outcome of osteoarthritis is unknown.[122-127] Because these drugs are relatively toxic to elderly patients—the population at risk for having osteoarthritis—it is prudent to use them in their lowest effective dosage and only if they relieve symptoms more than simple analgesics.

Administering steroids intra-articularly can reduce pain in joints affected by arthritis.[128] This would indicate that inflammation has a role in this process, but placebo responses could also account for some of the "successes" of intra-articular steroid use in this disorder. Intra-articularly or parenterally administered steroids could affect chondrocyte metabolism and the production of cytokines and proteolytic enzymes, but studies of the effects of such treatment on experimental osteoarthritis give conflicting results.[129-138] Conceivably intra-articular steroid use could hasten the progression of the disease, but at least one study indicates that it takes less steroid to suppress chondrocyte protease synthesis than to suppress proteoglycan synthesis.[138]

Chloroquine and doxycycline can inhibit the production or activity of chondrolytic enzymes.[139] Calcitonin has anabolic effects in chondrocytes and can stimulate cartilage growth.[25] Although these substances have shown some promise in experimental models, it remains to be seen whether they will benefit patients with established osteoarthritis. Unfortunately, the positive results from the intra-articular administration of a chondroprotective agent such as hyaluronan[141-143] could not be duplicated in a recent controlled trial.[144] Applied topically, capsaicin, which depletes local sensory nerve terminals of substance P, can reduce pain and tenderness in small joints affected by osteoarthritis.[145,146] The long-term effects of such therapy are unknown.

Most patients with osteoarthritis will never need surgical treatment of their joints, but when pain is unrelenting or when joint function is severely compromised, such treatment can provide substantial benefit. The most gratifying results have come from remodeling or replacing a hip or knee. Surgical therapy is rarely necessary for osteoarthritis of the hand, but occasionally a patient may benefit from fusing, resecting, or replacing a joint. Similar procedures are helpful when the disease causes severe pain or deformity in the feet.

Arthroscopic debridement—trimming meniscal fragments, removing loose debris, shaving shaggy articular surfaces—may relieve symptoms in some patients with

disease of the knee. Abrading the articular surface does not offer any additional benefit.[147] Some investigators advocate lavaging the knee by means of an arthroscope or cannula in an attempt to remove phlogistic debris.[148] The long-term results of such treatment are unknown.

The Challenge

To meet the challenge of this disease, we must clarify the factors leading to its onset and progression and devise safe and practical methods of preserving cartilage and relieving pain. The recent report that cultured autologous chondrocytes can be used to repair deep cartilage defects is a step in the right direction.[149]

REFERENCES

1. Price T, Hesp R, Mitchell R: Bone density in generalized osteoarthritis. J Rheumatol 1987; 14:560-562

2. Knight SM, Ring EF, Bhalla AK: Bone mineral density and osteoarthritis. Ann Rheum Dis 1992; 51:1025-1026

3. Howell DS, Sapolsky AI, Pita JC, Woessner F: The pathogenesis of osteoarthritis. Semin Arthritis Rheum 1976; 4:365-383

4. Hernborg J, Nilsson BE: The relationship between osteophytes in the knee joint, osteoarthritis and aging. Acta Orthop Scand 1973; 44:69-74

5. Hadler NM: Knee pain is the malady—Not osteoarthritis. Ann Intern Med 1992; 116:598-599

6. Kaye JJ: Radiologic assessment of osteoarthritis—New techniques. Rheum Dis Clin North Am 1993; 19:659-672

7. Davis MA, Ettinger WH, Neuhaus JM, Barclay JD, Segal MR: Correlates of knee pain among US adults with and without radiographic knee osteoarthritis. J Rheumatol 1992; 19:1943-1949

8. Peterfy CG, Majumdar S, Lang P, van Dijke CF, Sack K, Genant HK: MR imaging of the arthritic knee: Improved discrimination of cartilage, synovium, and effusion with pulsed saturation transfer and fat-suppressed T1-weighted sequences. Radiology 1994; 191:413-419

9. Lawrence JS, Bremner JM, Bier F: Osteoarthritis—Prevalence in the population and relationship between symptoms and x-ray changes. Ann Rheum Dis 1966; 25:1-24

10. Felson DT: Osteoarthritis. Rheum Dis Clin North Am 1990; 16:499-512

11. Anderson JJ, Felson DT: Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I)—Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988; 128:179-189

12. Hoaglund FT, Yau AC, Wong WL: Osteoarthritis of the hip and other joints in southern Chinese in Hong Kong. J Bone Joint Surg (Am) 1973; 55:645-657

13. Lawrence J, Sebo M: The geography of osteoarthritis, *In* Nuki G (Ed): The Aetiopathogenesis of Osteoarthritis. Baltimore, Md, University Park Press, 1958, pp 155-183

14. Stecher R: Heberden's nodes—A disease description of osteoarthritis in the finger joint. Ann Rheum Dis 1955; 14:1-10

15. Radin EL, Parker HG, Paul IL: Pattern of degenerative arthritis—Preferential involvement of distal finger-joints. Lancet 1971; 1:377-379

16. Hadler NM, Gillings DB, Imbus HR, et al: Hand structure and function in an industrial setting. Arthritis Rheum 1978; 21:210-220

17. Crain D: Interphalangeal osteoarthritis. JAMA 1961; 175:1049-1053

18. Ehrlich GE: Inflammatory osteoarthritis—I. The clinical syndrome. J Chronic Dis 1972; 25:317-328

19. Belhorn LR, Hess EV: Erosive osteoarthritis. Semin Arthritis Rheum 1993; 22:298-306

20. Brandt KD, Fife RS: Ageing in relation to the pathogenesis of osteoarthritis. Clin Rheum Dis 1986; 12:117-130

21. Greenwald RA, Moy WW, Seibold J: Functional properties of cartilage proteoglycans. Semin Arthritis Rheum 1978; 8:53-67

22. Hardingham TE, Bayliss M: Proteoglycans of articular cartilage: Changes in aging and in joint disease. Semin Arthritis Rheum 1990; 20(suppl 1):12-33

23. Yoshida K, Azuma H: Contents and compositions of glycosaminoglycans in different sites of the human hip joint cartilage. Ann Rheum Dis 1982; 41:512-519

24. Kiviranta I, Jurvelin J, Tammi M, Säämänen AM, Helminen HJ: Weight bearing controls glycosaminoglycan concentration and articular cartilage thickness in the knee joints of young beagle dogs. Arthritis Rheum 1987; 30:801-809

25. Howell DS, Altman RD: Cartilage repair and conservation in osteoarthritis—A brief review of some experimental approaches to chondroprotection. Rheum Dis Clin North Am 1993; 19:712-724

26. Poole A: Cartilage in health and disease, *In* McCarty D, Koopman W (Eds): Arthritis and Allied Conditions—A Textbook of Rheumatology. Philadelphia, Pa, Lea & Febiger, 1993, pp 279-333

27. Pelletier JP, DiBattista JA, Roughley P, McCollum R, Martel-Pelletier J: Cytokines and inflammation in cartilage degradation. Rheum Dis Clin North Am 1993; 19:545-568

28. Pelletier JP, Roughley PJ, DiBattista JA, McCollum R, Martel-Pelletier J: Are cytokines involved in osteoarthritic pathophysiology? Semin Arthritis Rheum 1991; 20:(suppl 2):12-25

29. Palmoski MJ, Colyer RA, Brandt KD: Joint motion in the absence of normal loading does not maintain normal articular cartilage. Arthritis Rheum 1980; 23:325-334

30. Allen ME: Arthritis and adaptive walking and running. Rheum Dis Clin North Am 1990; 16:887-914

31. Radin EL, Burr DB: Hypothesis: Joints can heal. Semin Arthritis Rheum 1984; 13:293-302

32. Palmoski M, Perricone E, Brandt KD: Development and reversal of a proteoglycan aggregation defect in normal canine knee cartilage after immobilization. Arthritis Rheum 1979; 22:508-517

33. Salter RB, Simmonds DF, Malcolm BW, Rumble EJ, MacMichael D, Clements ND: The biological effect of continuous passive motion on the healing of full-thickness defects in articular cartilage. J Bone Joint Surg (Am) 1980; 62:1232-1251

34. Radin EL, Paul IL: Response of joints to impact loading—I. In vitro wear. Arthritis Rheum 1971; 14:356-362

35. Radin EL, Burr DB, Caterson B, Fyhrie D, Brown TD, Boyd RD: Mechanical determinants of osteoarthrosis. Semin Arthritis Rheum 1991; 21(suppl 2):12-21

36. Cooper C, McAlindon T, Coggon D, Egger P, Dieppe P: Occupational activity and osteoarthritis of the knee. Ann Rheum Dis 1994; 53:90-93

37. Belmonte-Serrano MA, Bloch DA, Lane NE, Michel BE, Fries JF: The relationship between spinal and peripheral osteoarthritis and bone density measurements. J Rheumatol 1993; 20:1005-1013

38. Hannan MT, Anderson JJ, Zhang Y, Levy D, Felson DT: Bone mineral density and knee osteoarthritis in elderly men and women—The Framingham Study. Arthritis Rheum 1993; 36:1671-1680

39. Radin EL, Swann DA, Paul IL, McGrath PJ: Factors influencing articular cartilage wear in vitro. Arthritis Rheum 1982; 25:974-980

40. Cumming RG, Klineberg RJ: Epidemiological study of the relation between arthritis of the hip and hip fractures. Ann Rheum Dis 1993; 52:707-710

41. Dequeker J: The relationship between osteoporosis and osteoarthritis. Clin Rheum Dis 1985; 11:271-296

42. Dedrick DK, Goldstein SA, Brandt KD, O'Connor BL, Goulet RW, Albrecht M: A longitudinal study of subchondral plate and trabecular bone in cruciate-deficient dogs with osteoarthritis followed up for 54 months. Arthritis Rheum 1993; 36:1460-1467

43. Hordon LD, Wright V, Smith MA: Bone mass in osteoarthritis. Ann Rheum Dis 1992; 51:823-825

44. Hochberg M, Lethbridge-Cejku M, Scott W Jr, Plato C, Tobin J: Appendicular bone mass and osteoarthritis of the hands in women: Data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1994; 21:1532-1536

45. O'Connor BL, Brandt KD: Neurogenic factors in the etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am 1993; 19:581-605

46. Kellgren J, Moore R: Generalized osteoarthritis and Heberden's nodes. BMJ 1952; 1:181-187

47. Kellgren J, Lawrence J: Osteo-arthrosis and disk degeneration in an urban population. Ann Rheum Dis 1958; 17:388-397

48. Lawrence J: Generalized osteoarthrosis in a population sample. Am J Epidemiol 1960; 90:381-389

49. Stecher R: Heberden oration: Heberden's nodes—A clinical description of osteo-arthritis of the finger joints. Ann Rheum Dis 1955; 14:1-10

50. Stecher R, Hersh A, Hauser H: Heberden's nodes—The family history and radiographic appearance of a large family. Am J Hum Genet 1953; 5:46-60

51. Lawrence J, Gelsthorpe K, Morell G: Heberden's nodes and HLA markers in generalized osteoarthritis. J Rheumatol 1983; 10(suppl 9):32-33

52. Katzenstein PL, Malemud CJ, Pathria MN, Carter JR, Sheon RP, Moskowitz RW: Early-onset primary osteoarthritis and mild chondrodysplasia: Radiographic and pathologic studies with an analysis of cartilage proteoglycans. Arthritis Rheum 1990; 33:674-684

53. Ala-Kokko L, Baldwin CT, Moskowitz RW, Prockop DJ: Single base mutation in the type II procollagen gene (COL2A1) as a cause of primary osteoarthritis associated with a mild chondrodysplasia. Proc Natl Acad Sci USA 1990; 87:6565-6568

54. Vikkula M, Nissilä M, Hirvensalo E, et al: Multiallelic polymorphism of the cartilage collagen gene: No association with osteoarthrosis. Ann Rheum Dis 1993; 52:762-764

55. Rosner IA, Goldberg VM, Moskowitz RW: Estrogens and osteoarthritis. Clin Orthop 1986; (213):77-83

56. Young PC, Stack MT: Estrogen and glucocorticoid receptors in adult canine articular cartilage. Arthritis Rheum 1982; 25:568-573

57. Rosner IA, Manni A, Malemud CJ, Boja B, Moskowitz RW: Estradiol receptors in articular chondrocytes. Biochem Biophys Res Commun 1982; 106:1378-1382

58. Sheridan P, Aufdemorte T, Holt G, Gates G: Cartilage of the baboon contains estrogen receptors. Rheum Int 1985; 5:279-281

59. Silberberg M, Silberberg R: Modifying action of estrogen on the evaluation of osteoarthritis in mice of different ages. J Endocrinol 1963; 72:449-451

60. Rosner IA, Goldberg VM, Getzy L, Moskowitz RW: Effects of estrogen on cartilage and experimentally induced osteoarthritis. Arthritis Rheum 1979; 22:52-58

61. Chander CL, Spector TD: Oestrogens, joint disease and cartilage. Ann Rheum Dis 1991; 50:139-140

62. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF: Obesity and knee osteoarthritis—The Framingham Study. Ann Intern Med 1988; 109:18-24

63. Kohatsu ND, Schurman DJ: Risk factors for the development of osteoarthrosis of the knee. Clin Orthop 1990; (261):242-246

64. Davis MA, Ettinger WH, Neuhaus JM: Obesity and osteoarthritis of the knee: Evidence from the National Health and Nutrition Examination Survey (NHANES I). Semin Arthritis Rheum 1990; 20(suppl 1):34-41

65. Felson DT: The epidemiology of knee osteoarthritis: Results from the Framingham Osteoarthritis Study. Semin Arthritis Rheum 1990; 20(suppl 1):42-50

66. Cooper C, McAlindon T, Snow S, et al: Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: Differences between medial tibiofemoral and patellofemoral disease. J Rheumatol 1994; 21:307-313

67. Hart DJ, Spector TD: The relationship of obesity, fat distribution and osteoarthritis in women in the general population—The Chingford Study. J Rheumatol 1993; 20:331-335

68. Silberberg M, Silberberg R: Effects of a high fat diet on the joints of aging mice. Arch Pathol 1950; 50:828-846

69. Silberberg M, Jarrett S, Silberberg R: Obesity and degenerative joint disease. Arch Pathol 1956; 61:280-288

70. Silberberg M, Silberberg R: Osteoarthrosis in mice fed diets enriched with animal or vegetable fat. Arch Pathol 1960; 70:381-390

71. Sokoloff L, Mickelsen O: Dietary fat supplements, body weight and osteoarthritis in DBA/2JN mice. Nutrition 1965; 85:117-121

72. Sokoloff L: Endemic forms of osteoarthritis. Clin Rheum Dis 1985; 11:187-202

73. Sokoloff L: Kashin-Beck disease. Rheum Dis Clin North Am 1987; 13:101-104

74. Zhang GQ, Liu JX: An experimental animal model of Kashin-Beck disease. Ann Rheum Dis 1989; 48:149-152

75. Williams WV, Cope R, Gaunt WD, et al: Metacarpophalangeal arthropathy associated with manual labor (Missouri metacarpal syndrome)—Clinical, radiographic, and pathologic characteristics of an unusual degeneration process. Arthritis Rheum 1987; 30:1362-1371

76. Doherty M, Preston B: Primary osteoarthritis of the elbow. Ann Rheum Dis 1989; 48:743-747

77. Neer CS 2d, Craig EV, Fukuda H: Cuff-tear arthropathy. J Bone Joint Surg (Am) 1983; 65:1232-1244

78. McCarty DJ, Halverson PB, Carrera GF, Brewer BJ, Kozin F: 'Milwaukee shoulder'—Association of microspheroids containing hydroxyapatite crystals, active collagenase, and neutral protease with rotator cuff defects—I. Clinical aspects. Arthritis Rheum 1981; 24:464-473

79. Bland JH: Diagnosis and treatment of osteoarthritis. Curr Opin Rheumatol 1989; 1:315-324

80. Bland JH, Boushey DR: Anatomy and physiology of the cervical spine. Semin Arthritis Rheum 1990; 20:1-20

81. Harfing J, Halla J: Cervical spine syndromes, *In* McCarty D, Koopman W (Eds): Arthritis and Allied Conditions—A Textbook of Rheumatology. Philadelphia, Pa, Lea & Febiger, 1993, pp 1563-1571

82. Cushnaghan J, Dieppe P: Study of 50 patients with limb joint osteoarthritis—I. Analysis by age, sex, and distribution of symptomatic joint sites. Ann Rheum Dis 1991; 50:8-13

83. Croft P, Coggon D, Cruddas M, Cooper C: Osteoarthritis of the hip: An occupational disease in farmers. BMJ 1992; 304:1269-1272

84. Hoaglund FT, Shiba R, Newberg AH, Leung KY: Diseases of the hip. J Bone Joint Surg (Am) 1985; 67:1376-1383

85. Felson DT, Naimark A, Anderson JJ, Kazis L, Castelli W, Meenan RF: The prevalence of knee osteoarthritis in the elderly—The Framingham Osteoarthritis Study. Arthritis Rheum 1987; 30:914-918

86. Felson DT, Radin EL: What causes knee osteoarthrosis: Are different compartments susceptible to different risk factors? J Rheumatol 1994; 21:181-183

87. Lane NE, Buckwalter JA: Exercise: A cause of osteoarthritis? Rheum Dis Clin North Am 1993; 19:617-633

88. Hannan MT, Felson DT, Anderson JJ, Naimark A: Habitual physical activity is not associated with knee osteoarthritis: The Framingham Study. J Rheumatol 1993; 20:704-709

89. Panush RS: Does exercise cause arthritis?—Long-term consequences of exercise on the musculoskeletal system. Rheum Dis Clin North Am 1990; 16:827-836

90. Hutton CW: Generalised osteoarthritis: An evolutionary problem? Lancet 1987; 1:1463-1465

91. Hutton CW: Osteoarthritis: The cause not result of joint failure? Ann Rheum Dis 1989; 48:958-961

92. Peter JB, Pearson CM, Marmor L: Erosive osteoarthritis of the hands. Arthritis Rheum 1966; 9:365-388

93. Cobby M, Cushnaghan J, Creamer P, Dieppe P, Watt I: Erosive osteoarthritis: Is it a separate disease entity? Clin Radiol 1990; 42:258-263

94. Altman RD, Gray R: Inflammation in osteoarthritis. Clin Rheum Dis 1985; 11:353-365

95. Ehrlich GE: Osteoarthritis beginning with inflammation—Definitions and correlations. JAMA 1975; 232:157-159

96. Doherty M, Pattrick M, Powell R: Nodal generalised osteoarthritis is an autoimmune disease. Ann Rheum Dis 1990; 49:1017-1020

97. Sack KE: Osteoarthritis: Cause and long-term management. Compr Ther 1982; 8:46-51

98. Gibilisco PA, Schumacher HR Jr, Hollander JL, Soper KA: Synovial fluid crystals in osteoarthritis. Arthritis Rheum 1985; 28:511-515

99. Schumacher HR Jr: Crystals, inflammation, and osteoarthritis. Am J Med 1987; 83(5A):11-16

100. Blackburn WD Jr, Bernreuter WK, Rominger M, Loose LL: Arthroscope evaluation of knee articular cartilage: A comparison with plain radiographs and magnetic resonance imaging. J Rheumatol 1994; 21:675-679

101. Fife RS, Brandt KD, Braunstein EM, et al: Relationship between arthroscopic evidence of cartilage damage and radiographic evidence of joint space narrowing in early osteoarthritis of the knee. Arthritis Rheum 1991; 34:377-382

102. Ledingham J, Dawson S, Preston B, Milligan G, Doherty M: Radiographic progression of hospital referred osteoarthritis of the hip. Ann Rheum Dis 1993; 52:263-267

103. Chan WP, Lang P, Stevens MP, et al: Osteoarthritis of the knee: Comparison of radiography, CT, and MR imaging to assess extent and severity. AJR Am J Roentgenol 1991; 157:799-806

104. Kallir O: Grandma Moses—My Life's History. New York, NY, Harper & Brothers, 1952

105. Baron M, Dutil E, Berkson L, Lander P, Becker R: Hand function in the elderly: Relation to osteoarthritis. J Rheumatol 1987; 14:815-819

106. Pattrick M, Aldridge S, Hamilton E, Manhire A, Doherty M: A controlled study of hand function in nodal and erosive osteoarthritis. Ann Rheum Dis 1989; 48:978-982

107. Forman MD, Malamet R, Kaplan D: A survey of osteoarthritis of the knee in the elderly. J Rheumatol 1983; 10:282-287

108. Felson DT: The course of osteoarthritis and factors that affect it. Rheum Dis Clin North Am 1993; 19:607-615

109. René J, Weinberger M, Mazzuca SA, Brandt KD, Katz BP: Reduction of joint pain in patients with knee osteoarthritis who have received monthly telephone calls from lay personnel and whose medical treatment regimens have remained stable. Arthritis Rheum 1992; 35:511-515

110. Neumann DA, Cook TM, Sholty RL, Sobush DC: An electromyographic analysis of hip abductor muscle activity when subjects are carrying loads in one or both hands. Phys Ther 1992; 72:207-217

111. McAlindon TE, Cooper C, Kirwan JR, Dieppe PA: Determinants of disability in osteoarthritis of the knee. Ann Rheum Dis 1993; 52:258-262

112. Fisher NM, Pendergast DR, Gresham GE, Calkins E: Muscle rehabilitation: Its effect on muscular and functional performance of patients with knee osteoarthritis. Arch Phys Med Rehabil 1991; 72:367-374

113. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ: Weight loss reduces the risk for symptomatic knee osteoarthritis in women—The Framingham Study. Ann Intern Med 1992; 116:535-539

114. Yasuda K, Sasaki T: The mechanics of treatment of the osteoarthritic knee with a wedged insole. Clin Orthop 1987; (215):162-172

115. Bunning RD, Materson RS: A rational program of exercise for patients with osteoarthritis. Semin Arthritis Rheum 1991; 21 (suppl 2):33-43

116. Hadler NM: Osteoarthritis as a public health problem. Clin Rheum Dis 1985; 11:175-185

117. Altman RD, Dean D: Pain in osteoarthritis—Introduction and overview. Semin Arthritis Rheum 1989; 18(suppl 2):1-3

118. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991; 325:87-91

119. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI: Treatment of knee osteoarthritis: Relationship of clinical features of joint inflammation to the

response to a nonsteroidal antiinflammatory drug or pure analgesic. J Rheumatol 1992; 19:1950-1954

120. Dieppe P, Cushnaghan J, Jasani MK, McCrae F, Wan I: A two-year, placebo-controlled trial of non-steroidal anti-inflammatory therapy in osteoarthritis of the knee joint. Br J Rheumatol 1993; 32:595-600

121. Williams HJ, Ward JR, Egger MJ, et al: Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993; 36:1196-1206

122. Palmoski MJ, Colyer RA, Brandt KD: Marked suppression by salicylate of the augmented proteoglycan synthesis in osteoarthritic cartilage. Arthritis Rheum 1980; 23:83-91

123. Palmoski MJ, Brandt KD: Effects of some nonsteroidal antiinflammatory drugs on proteoglycan metabolism and organization in canine articular cartilage. Arthritis Rheum 1980; 23:1010-1020

124. Palmoski MJ, Brandt KD: Relationship between matrix proteoglycan content and the effects of salicylate and indomethacin on articular cartilage. Arthritis Rheum 1983; 26:528-531

125. Herman JH, Hess EV: Nonsteroidal anti-inflammatory drugs and modulation of cartilaginous changes in osteoarthritis and rheumatoid arthritis—Clinical implications. Am J Med 1984; 77(4B):16-25

126. Brandt KD: Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and in vivo. Am J Med 1987; 83(5A):29-34

127. Brandt KD: Should nonsteroidal anti-inflammatory drugs be used to treat osteoarthritis? Rheum Dis Clin North Am 1993; 19:29-44

128. Hollinder J: Osteoarthritis: Perspectives on treatment. Postgrad Med 1980; 68:161-168

129. Behrens F, Shepard N, Mitchell N: Alterations of rabbit articular cartilage by intra-articular injections of glucocorticoids. J Bone Joint Surg (Am) 1975; 57:70-76

130. Behrens F, Shepard N, Mitchell N: Metabolic recovery of articular cartilage after intra-articular injections of glucocorticoid. J Bone Joint Surg (Am) 1976; 58:1157-1160

131. Silbermann M, von der Mark K, Maor G, van Menxel M: Dexamethasone impairs growth and collagen synthesis in condylar cartilage in vitro. Bone Miner 1967; 2:87-98

132. Myers SL, Brandt KD, O'Connor BL: Low dose prednisone treatment does not reduce the severity of osteoarthritis in dogs after anterior cruciate ligament transection. J Rheumatol 1991; 18:1856-1862

133. Butler M, Colombo C, Hickman L, et al: A new model of osteoarthritis in rabbits—Evaluation of anti-osteoarthritic effects of selected drugs administered intraarticularly. Arthritis Rheum 1983; 26:1380-1386

134. Pelletier JP, Martel-Pelletier J, Cloutier JM, Woessner JF Jr: Proteoglycan-degrading acid metalloprotease activity in human osteoarthritic cartilage, and the effect of intraarticular steroid injections. Arthritis Rheum 1987; 30:541-548

135. Pelletier JP, Martel-Pelletier J: Protective effects of corticosteroids on cartilage lesions and osteophyte formation in the Pond-Nuki dog model of osteoarthritis. Arthritis Rheum 1989; 32:181-193

136. van der Kraan PM, Vitters EL, Postma NS, Verbunt J, van den Berg WB: Maintenance of the synthesis of large proteoglycans in anatomically intact murine articular cartilage by steroids and insulin-like growth factor I. Ann Rheum Dis 1993; 52:734-741

137. Pelletier JP, Mineau F, Raynauld JP, Woessner JF Jr, Gunja-Smith Z, Martel-Pelletier JP: Intraarticular injections with methylprednisolone acetate reduce osteoarthritic lesions in parallel with chondrocyte stromelysin synthesis in experimental osteoarthritis. Arthritis Rheum 1994; 37:414-423

138. Pelletier JP, Cloutier JM, Martel-Pelletier J: In vitro effects of tiaprofenic acid, sodium salicylate and hydrocortisone on the proteoglycan metabolism of human osteoarthritic cartilage. J Rheumatol 1989; 16:646-655

139. Fife R, Brandt KD: Other approaches to therapy, *In* Moskowitz R, Howell D, Goldberg V, Mankin H (Eds): Osteoarthritis: Diagnosis and Medical/Surgical Management, 2nd edition. Philadelphia, Pa, WB Saunders, 1992, pp 511-526

140. Yu LP Jr, Smith GN Jr, Brandt KD, Myers SL, O'Connor BL, Brandt DA: Reduction of the severity of canine osteoarthritis by prophylactic treatment with oral doxycycline. Arthritis Rheum 1992; 35:1150-1159

141. Abatangelo G, Botti P, Del Bue M, et al: Intraarticular sodium hyaluronate injections in the Pond-Nuki experimental model of osteoarthritis in dogs—I. Biochemical results. Clin Orthop 1989; (241):278-285

142. Schiavinato A, Lini E, Guidolin D, et al: Intraarticular sodium hyaluronate injections in the Pond-Nuki experimental model of osteoarthritis in dogs—II. Morphological findings. Clin Orthop 1989; (241):286-299

143. Peyron JG: Intraarticular hyaluronan injections in the treatment of osteoarthritis: State-of-the-art review. J Rheumatol Suppl 1993; 39:10-15

144. Dahlberg L, Lohmander LS, Ryd L: Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain—A one-year double-blind, placebo-controlled study. Arthritis Rheum 1994; 37:521-528

145. McCarthy GM, McCarty DJ: Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. J Rheumatol 1992; 19:604-607

146. Altman R, Aven A, Holmburg C, Pfeifer L, Sack M, Young G: Capsaicin cream 0.025% as monotherapy for osteoarthritis: A double-blind study. Semin Arthritis Rheum 1994; 23(suppl 3):25-33

147. Bert JM: Role of abrasion arthroplasty and debridement in the management of osteoarthritis of the knee. Rheum Dis Clin North Am 1993; 19:725-739

148. Ike RW, Arnold WJ, Rothschild EW, et al: Tidal irrigation versus conservative medical management in patients with osteoarthritis of the knee: A prospective randomized study—Tidal Irrigation Cooperating Group. J Rheumatol 1992; 19:772-779

149. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L: Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 1994; 331:889-895

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